REMARKS

Status of Claims

Claims 1-4, 7-8, 11-13, 16-17, and 20-21 are currently pending in the application.

Solely to expedite prosecution, claims 1-4, 7-8, 11, 13, 16-17, and 20-21 have been amended to remove the term "or ester" thereof as it refers to esters of DMXAA, thereby obviating the Examiner's rejection of these claims as lacking written description for this terminology. Applicants reserve the right to take whatever action is necessary to preserve the subject matter removed by these amendments to the claims.

Claims 3, 8, 13, and 17 have been amended to change "the gemcitabine" to "gemcitabine," in compliance with the Examiner's objection that "the" is not required as a modifier for "gemcitabine." Applicants thank the Examiner for bringing this more appropriate terminology to their attention.

The above amendments to the claims are supported by the specification as originally filed. No new matter has been added by way of these amendments.

Priority To Foreign Priority Document GB0121285.1 Should Be Granted

The Examiner has indicated that the claim by Applicants to the foreign priority document GB0121285.1 has not been granted because Applicants have not filed a certified copy of this document. In this regard, Applicants note that Rule 17.2(a) of the Patent Cooperation Treaty states, *inter alia*, that:

> Where the applicant has complied with Rule 17.1(a), (b) or (b-bis) the International Bureau shall, at the specific request of the designated Office, promptly but not prior to the international publication of the international application, furnish a copy of the priority document to that Office. **No such**

Office shall ask the applicant himself to furnish it with a copy. (emphasis added).

Therefore, on this basis, Applicants have complied with all requirements necessary to establish a priority date to foreign priority document GB0121285.1, and the Examiner should grant foreign priority to the above-referenced document.

The Objection To The Claims Has Been Obviated, And Should Be Withdrawn

The Examiner has pointed out that claims 3, 4, 8, 13, and 17 contain the phrase "the gemcitabine," and that the word "the" is not required in referring to gemcitabine. Applicants thank the Examiner for identifying this correction to Applicants, and have now amended claims 3, 8, 13, and 17 in keeping with the Examiner's statements. Applicants note that in fact claim 4 did not state "the gemcitabine," but rather the preferable phrase "gemictabine"; therefore, no amendment to this claim was required.

The Rejection Of The Claims Under 35 U.S.C. § 112, First Paragraph, As Lacking Written Description Has Been Obviated, And Should Be Withdrawn

The Examiner has rejected claims 1-4, 7-8, 11, 13, 16-17, and 20-21 as lacking written description for the inclusion not only of DMXAA, but of also esters of DMXAA. Although Applicants respectfully disagree with the Examiner's conclusions, in order to expedite prosecution, Applicants have now amended the rejected claims to remove all references to esters of DMXAA. Therefore, on this basis, the Examiner's rejection of these claims as lacking written description for this terminology has been obviated, and this rejection should be withdrawn.

The Rejection Of The Claims Under 35 U.S.C. § 103(a) Has Been Obviated, And Should Be Withdrawn

The Examiner has rejected claims 1-4, 7-8, 11-13, 16-17, and 20-21 under 35 U.S.C. § 103(a) as obvious over Siemann et al. ("Siemann") in view of Pruijn et al. ("Pruijn") and van Moorsel et al. ("van Moorsel"). Specifically, the Examiner argues that: 1) Siemann teaches DMXAA in combination with cisplatin or cyclophosphamide; 2) Pruijn teaches DMXAA in combination with melphalan; 3) van Moorsel teaches gemcitabine in combination with etoposide; and, therefore, 4) in light of the fact that DMXAA is used with other chemotherapeutics (see Siemann or Pruijn) and the fact that gemcitabine is used in combination with other chemotherapeutics (see van Moorsel), it would be obvious to one of ordinary skill to combine DMXAA with gemcitabine, as is done in the present invention. These arguments may be summarized in tabular form as:

	DMXAA	Gemcitabine	Cisplatin	Cyclophosphamide	Melphalan	Etoposide
Siemann	X		X	X		
Pruijn	X				X	
van Moorsel		X				X
Invention	X	X				

With regard to this rejection, Applicants respectfully note that there can be absolutely no basis to obtain the combination of the invention of DMXAA and gemcitabine based on Siemann, Pruijn, or van Moorsel, alone or in combination, since the *mere fact* that these references teach that DMXAA can be used with cisplatin/cyclophosphamide/melphalan and the *mere fact* these references teach that gemictabine can be used with etoposide do not in any way make obvious the specific nonobvious combination of DMXAA and gemcitabine of the present invention.

As an example, Applicants note that cisplatin/cyclophosphamide/melphalan are all crosslinking agents. Gemcitabine is not a crosslinking agent; therefore there is no basis on which one of ordinary skill would think to use gemcitabine instead of

cisplatin/cyclophosphamide/melphalan, thereby obtaining the combination of the invention of DMXAA and gemcitabine. Similar arguments may be made for the use of etoposide, which is, by the Examiner's own statement "a widely used anticancer agent that inhibits topoisomerase II." Office Action, page 6, end of first full paragraph.

Additionally, it appears that the Examiner's larger rationale in making this obviousness rejection of the claims is that the claims are obvious because "DMXAA and gemcitabine are individually known in the art as agents for treating cancers," and therefore their combination would be obvious based on case law provided in the *Manual of Patent Examining Procedure* (MPEP) § 2144.06, "Art Recognized Equivalence for the Same Purpose," and in particular on the case law provided in the first part of this section, "Combining Equivalents Known For The Same Purpose." Thus, drawing from this section of the MPEP, the Examiner states that the claims are obvious because:

> It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

See Office Action, page 7, middle of page.

With regard to this rejection of the claims, to argue that case law on the combination of two conventional spray-dried detergents (*Kerkohven*) or two well-known cast iron nodulizing agents (*Crockett*) is applicable to combinations of chemotherapeutics is, respectfully, an exercise in *reductio ad absurdum* (reduction to absurdity) which cannot be deemed applicable in the instant case.

Specifically, in both *Kerkhoven* and *Crockett* the compounds at issue were highly well known and interchangeable, so much so that, in the words of another case cited in MPEP § 2144.06, they were effectively "so notoriously well known as to be capable of being taken [in combination merely] by *official notice*" (emphasis added)(see *Ex parte Quadtranti*,

25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992), regarding the obviousness of combinations of two well known herbicides). Thus in *Kerkhoven* the court stated that the combination of spray-dried detergents was *prima facie* obvious because such combination required "*no more than* the mixing together of [the] two conventional spray-dried detergents" of the claims, *In re Kerkhoven,* 626 F.2d 486, 850 (emphasis added), while in *Crockett* the court stated that the claims called for "*nothing more than* an obvious combination of two old nodulizing materials," *In re Crockett*, 47 C.C.P.A. 1018, 1021 (emphasis added).

In contrast to the above, the claims of the instant invention are directed not to mere combinations of spray-dried detergents, or of cast iron nodulizing agents, or even of well known herbicides; instead, the claims of the present invention are directed to novel combinations of particular anti-cancer reagents which, when combined, are effective at treating particular cancers (i.e., solid cancers). To argue that these particular combinations of anti-cancer reagents selected to treat particular kinds of cancers are obvious on the same logical basis as well known and interchangeable spray-dried detergents, nodulizing agents, or plant-killing herbicides are obviously combined is -- at best -- wholly inapposite.

Furthermore, with regard to the Examiner's statement that there is a "natural presumption" that "two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer," Applicants respectfully request that the Examiner explain the basis of this "natural presumption" in light of, for example, the well-known *adverse* or even *lethal* effects of many combinations of anticancer agents. Thus an extremely brief review by Applicants attorney reveals that, for example, severe hand-foot syndrome results from the combination of capecitabine with docetaxel, an effect that was not expected prior to the administration of this combination of drugs to patients. See Park et al. Annals of Oncology 14:1691-1692 (2003), available at http://annonc.oxfordjournals.org/cgi/content/full/14/11/1691.

Additionally, the Examiner made a variety of arguments regarding synergy. In this regard, Applicants note that the application as filed provides evidence that, contrary to the assertion made by the Examiner, not all chemotherapeutics show synergy when used in

combination with DMXAA. For example, Table 1 of the application as filed demonstrates that no synergy is seen with a combination of 5-fluorouracil (5-FU) and DMXAA (this combination having, as described in the text preceding Table 1, a "DMF" value of less than 1).

As gemcitabine and 5-FU are both antimetabolites (indeed both are fluorinated pyrimidine analogues), then they might, in terms of their properties, be expected to be the amongst the most similar agents disclosed in the present application. However, the results listed in Table 1 show precisely how unpredictable synergy is and, contrary to the assertions made by the Examiner, quite how unexpected are the synergistic effects seen with the remaining anti-cancer agents listed in the present application.

In summary, in light of the arguments presented above, the Examiner has not presented sufficient evidence to support the requirements of a finding of obviousness under 35 U.S.C. § 103(a), and the rejection of the claims on this basis must be withdrawn.

CONCLUSION

In light of the above, Applicants submit that the rejections of the claims must be withdrawn and that the claims be allowed.

The Commissioner is hereby authorized to charge $450 for a two-month extension of time, and any other time extension or other fee that may have been overlooked by Applicants to Deposit Account No. 10-0223.

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